FDG-PET/CT as a Predictor of Outcome in EGFR-Mutant Non–Small-Cell Lung Cancer

Kathryn A. Gold, MD and Jeremy J. Erasmus, MD

Activating mutations in the epidermal growth factor receptor (*EGFR*) are found in approximately 10% to 15% of non–small-cell lung cancer (NSCLC) patients in the United States and up to 35% of those in East Asia.[1,2] Patients with this mutation are more likely to be female, Asian, and nonsmokers than the general lung cancer population. For patients with these mutations, treatment with *EGFR* tyrosine kinase inhibitors (TKIs) erlotinib, afatinib, or gefitinib is associated with higher response rates and improved progression-free survival (PFS) compared with standard platinum-based doublet chemotherapy.[3,4] Unfortunately, acquired resistance to these TKIs inevitably develops. A variety of resistance mechanisms have been identified, including a secondary mutation in *EGFR*, T790M.[5–7] Resistance to TKIs usually occurs at a median of 9 to 13 months after treatment initiation although there is a wide range. In this regard, some patients have progression of disease years after initiation of TKI therapy while others have rapid progression and widespread disease after only a few months. Currently, there are no reliable clinical tools to predict outcomes for patients with EGFR mutations treated with TKIs.

In this issue of the Journal of Thoracic Oncology, Keam et al. report on the relation between FDG-PET/CT metabolic parameters and outcomes in patients with *EGFR*-mutant lung cancer receiving gefitinib as first-line treatment at a single center in South Korea. Seventy-five patients with stage IIIB or IV chemotherapy naive NSCLC were identified from a retrospective database. All patients had one of the two most common activating *EGFR* mutations—either a deletion in exon 19 or the L858R missense mutation in exon 21. Patients with these mutations are known to respond well to EGFR TKIs.[1] Outcomes for patients enrolled on this trial were similar to historical controls, with an overall response rate of 69%, median PFS 11.5 months, and median overall survival (OS) 26.7 months.

Keam et al. performed whole-body FDG-PET/CT in all patients before initiation of therapy and found that total lesion glycolysis (TLG), a measure that reflects both tumor bulk and metabolic activity, was significantly associated with PFS and OS. Patients with the highest TLG had a PFS of only 7.2 months, compared with patients with low TLG with PFS 24.2 months. SUVmax was also associated with PFS, but the correlation was not as strong, and there was no significant association between SUVmax and OS. Interestingly, response rates were not different between those with high TLG and those with low TLG.

Similar to many retrospective studies, the temporal performance of the imaging in the study by Keam et al. was not standardized and there was a large range between the FDG-PET/CT acquisition and the initiation of gefitinib therapy (range 0–46 days, median 19 days). Because of the considerable variation of tumor metabolic activity at different time points, this inconsistency in the performance of the baseline FDG-PET/CT is a potential limitation of the applicability of the imaging analysis and conclusions drawn. In addition, in terms of methodology, the use of a single threshold (50% of SUVmax for each lesion) to determine volume is prone to error, primary due to the value being affected by lesion

The University of Texas MD Anderson Cancer Center, Houston, Texas.
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Address for correspondence: Kathryn A. Gold, MD, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Unit 0432, Houston, TX 77030. E-mail:kagold@mdanderson.org
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size and lesion to background (*L*/*B*) ratio. This error is further magnified when the lesions evaluated have a small size. Although lesion size and *L*/*B* ratio are not discussed by the investigators, more sophisticated approaches that take these factors into consideration are not generally available.

The results of the study by Keam et al. are interesting. However, the clinical applicability is currently somewhat limited. Even if it was possible to reliably identify patients likely to have shorter PFS on TKIs, it is not clear that treatment recommendations for these patients would change—erlotinib, gefitinib, and afatinib remain the agents of choice for patients with activating *EGFR* mutations. Also, this was a relatively small, single center study in Asian patients. Validation in a larger cohort, especially one incorporating patients from different geographic regions treated with different TKIs, would be helpful.

It is not surprising that patients with bulky, highly active lesions have poor outcomes compared with those patients with a small volume of disease. As the authors note, larger tumors may have more genetic heterogeneity; therefore, resistant clones may be more likely to be present at baseline and may become clinically apparent more quickly. Patients such as those with high TLG who are known to have a relatively poor prognosis with standard treatment should be evaluated for clinical protocols aiming to prevent emergence of resistant clones. Third generation EGFR inhibitors rociletinib and AZD9291 appear to be active in *EGFR*-mutant NSCLC resistant to first-line TKIs, especially in tumors with T790M resistance mutations.[8,9] Ongoing studies (NCT02186301, NCT02296125) are comparing these agents to erlotinib or gefitnib for treatment naive patients with *EGFR*-mutant NSCLC, in hopes that these newer agents may delay the emergence of resistance.

In summary, although significant strides have been made recently in the treatment of *EGFR*-mutant NSCLC, there is still work to be done. Keam et al. have contributed to this undertaking by elucidating that high TLG can predict PFS and development of gefitinib resistance in *EGFR*-mutant NSCLC patients treated with first-line gefitinib. Their study underlines the urgent need for new novel therapeutics, especially for those patients identified as having poor outcomes.

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